

A dynamic p53-mdm2 model with distributed time delay

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Abstract

The objective of this paper is to investigate the stability of limit cycles of a mathematical model with a distributed delay which describes the interaction between p53 and mdm2. Choosing the delay as a bifurcation parameter we study the direction and stability of the bifurcating periodic solutions using the normal form and the center manifold theorem. Some numerical examples are finally made in order to confirm the theoretical results.

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1. Introduction

The tumor suppresser gene p53 plays a key role in oncogenesis and its anomalies are almost universal in tumoral cells [4]. To make the reading easier we briefly present the role of p53 gene in living cells. Normally the activity of p53 is inhibited and the concentration of p53 protein are kept at very low levels. The activation occurs when there are DNA damages [2,3]. Depending on these damages there are two outcomes: one is the cell cycle arrest induced by a low level or a brief elevation of p53 protein, and the other is the apoptosis induced by a high level or a prolonged elevation of p53 protein [5]. Knowing these 2 different outcomes, it is now clear that the level of p53 protein should be kept tight control. This control is achieved with the help of mdm2 gene with which p53 makes a feedback loop [5, 10]. Recently it had been discovered that this loop is not quite straightforward because there are two isoforms of the mdm2 protein, i.e. p76mdm2 and p90mdm2 which have different features and roles [7].

This new model is based on [8, 9]. Here we achieve a smoother modeling of the phenomenon, i.e. the interaction p53-mdm2. The production of p53 protein is continuous, so is the binding between p53 and the promoter of the mdm2. The difference from the previous model [9] lies in the introduction of the integral form in the third equation, which is the natural way of modeling a continuous process. To have a clear picture of this aspect, we explain the need for the introduction of the integral form, by the fact that the synthesis of p53 protein and the binding p53-mdm2 are continuous and there is no buffer to store p53 and then, at a given moment, to release it, and after that all the quantity of p53 to bind mdm2 promoter. As a matter of fact, the molecules of p53 protein that are bound with mdm2 promoter were not synthesized at the moment t , but they were synthesized at a previous different moments, they were bound at different moments.

The variables of the model are: x_1 , x_2 mRNA concentrations and y_1 , y_2 the protein concentrations.

The mathematical system which describes our model is:

$$\begin{aligned}
\dot{x}_1(t) &= 1 - b_1 x_1(t), \\
\dot{y}_1(t) &= x_1(t) - (a_1 + a_{12} y_2(t)) y_1(t), \\
\dot{x}_2(t) &= \frac{1}{\tau} \int_0^\tau (\alpha f(y_1(t)) + (1 - \alpha) f(y_1(t - s))) ds - b_2 x_2(t), \\
\dot{y}_2(t) &= x_2(t) - (a_2 + a_{12} y_1(t)) y_2(t)
\end{aligned} \tag{1}$$

where: b_1, b_2 are the rates for mRNA degradation, a_1, a_2, a_{12} are the rates for protein degradation. The function $f : \mathbb{R}_+ \rightarrow \mathbb{R}$, is the Hill function, given by:

$$f(x) = \frac{x^n}{a + x^n} \tag{2}$$

with $n \in \mathbb{N}^*, a > 0$. The parameters $a_1, a_2, b_1, b_2, a_{12}$ of the model are assumed to be positive numbers less or equal to 1, $\alpha \in [0, 1]$ and $\tau \geq 0$.

For $\alpha = 0$ in the present model, we obtain the model from [9], which suggests that there is an oscillatory behavior based on using only numerical simulations.

For the study of the model (1) we consider the following initial values:

$$x_1(0) = \bar{x}_1, y_1(\theta) = \varphi_1(\theta), \theta \in [-\tau, 0], x_2(0) = \bar{x}_2, y_2(0) = \bar{y}_2,$$

with $\bar{x}_1 \geq 0, \bar{x}_2 \geq 0, \bar{y}_2 \geq 0, \varphi_1(\theta) \geq 0$, for all $\theta \in [-\tau, 0]$ and φ_1 is a differentiable function.

The paper is organized as follows. In section 2, we discuss the local stability for the equilibrium state of system (1). We investigate the existence of the Hopf bifurcation for system (1) using time delay as the bifurcation parameter. In section 3, the direction of Hopf bifurcation is analyzed by the normal form theory and the center manifold theorem introduced by Hassard [6]. Numerical simulations for justifying the theoretical results are illustrated in section 4. Finally, some conclusions are made and further research directions are presented.

2. Local stability and the existence of the Hopf bifurcation.

The equilibrium points of system (1) are given by the solutions of the following system of equations:

$$\begin{aligned}
1 - b_1 x_1(t) &= 0, \\
x_1(t) - (a_1 + a_{12} y_2(t)) y_1(t) &= 0, \\
f(y_1(t)) - b_2 x_2(t) &= 0, \\
x_2(t) - (a_2 + a_{12} y_1(t)) y_2(t) &= 0.
\end{aligned} \tag{3}$$

Let $g : (0, \infty) \rightarrow \mathbb{R}$ be the function given by:

$$g(x) = \frac{(a_2 + a_{12} x)(1 - a_1 b_1 x)}{b_1 a_{12} x}. \tag{4}$$

From (3) and (4) it results that one solution of system (3) is:

$$x_1 = \frac{1}{b_1}, \quad y_1, \quad x_2 = \frac{(a_2 + a_{12} y_1)(-a_1 b_1 y_1 + 1)}{b_1 a_{12} y_1}, \quad y_2 = \frac{-a_1 b_1 y_1 + 1}{b_1 a_{12} y_1}, \tag{5}$$

where y_1 is the solution of the equation:

$$f(x) - g(x) = 0. \tag{6}$$

Because $f(x)$ is an increasing function with $\lim_{x \rightarrow \infty} f(x) = 1$ then $g(x)$ is an increasing function too, for $x < \frac{1}{a_1 b_1}$. It results that equation (6) has a unique solution.

Proposition 1. *If y_{10} is a real solution of (6) then the equilibrium point of system (1) is:*

$$x_{10} = \frac{1}{b_1}, \quad y_{20} = \frac{1 - a_1 b_1 y_{10}}{b_1 a_{12} y_{10}}, \quad x_{20} = \frac{(a_2 + a_{12} y_{10})(1 - a_1 b_1 y_{10})}{b_1 a_{12} y_{10}}. \tag{7}$$

We consider the following translation:

$$x_1 = u_1 + x_{10}, \quad y_1 = u_2 + y_{10}, \quad x_2 = u_3 + x_{20}, \quad y_2 = u_4 + y_{20}. \tag{8}$$

With respect to (8), system (1) can be expressed as:

$$\begin{aligned}
\dot{u}_1(t) &= -b_1 u_1(t), \\
\dot{u}_2(t) &= u_1(t) - (a_1 + a_{12} y_{20}) u_2(t) - a_{12} y_{10} u_4(t) - a_{12} u_2(t) u_4(t), \\
\dot{u}_3(t) &= \frac{1}{\tau} \int_0^\tau (\alpha f(u_2(t) + y_{10}) + (1 - \alpha) f(u_2(t - s) + y_{10})) ds - b_2 u_3(t) - b_2 x_{20}, \\
\dot{u}_4(t) &= -a_{12} y_{20} u_2(t) + u_3(t) - (a_2 + a_{12} y_{10}) u_4(t) - a_{12} u_2(t) u_4(t).
\end{aligned} \tag{9}$$

System (9) has $(0, 0, 0, 0)$ as equilibrium point.

To investigate the local stability of the equilibrium state we linearize system (9). We expand it in a Taylor series around the origin and neglect the terms of higher order than the first order for the functions from the right side of (9). We obtain:

$$\dot{U}(t) = AU(t) + \frac{1}{\tau}B \int_0^\tau U(t-s)ds, \quad (10)$$

where

$$A = \begin{pmatrix} -b_1 & 0 & 0 & 0 \\ 1 & -(a_1 + a_{12}y_{20}) & 0 & -a_{12}y_{10} \\ 0 & \alpha\rho_1 & -b_2 & 0 \\ 0 & -a_{12}y_{20} & 1 & -(a_2 + a_{12}y_{10}) \end{pmatrix}, B = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & (1-\alpha)\rho_1 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \quad (11)$$

with $\rho_1 = f'(y_{10})$, $U(t) = (u_1(t), u_2(t), u_3(t), u_4(t))^T$, $\int_0^\tau U(t-s)ds = (\int_0^\tau u_1(t-s)ds, \int_0^\tau u_2(t-s)ds, \int_0^\tau u_3(t-s)ds, \int_0^\tau u_4(t-s)ds)^T$.

The characteristic equation corresponding to system (10) is $\det(\lambda I - A - (\frac{1}{\tau} \int_0^\tau e^{-\lambda s} ds)B) = 0$ which leads to:

$$(\lambda + b_1)(\lambda^3 + b\lambda^2 + c\lambda + d + \frac{h}{\tau} \int_0^\tau e^{-\lambda s} ds) = 0, \quad (12)$$

where

$$\begin{aligned} b &= a_1 + a_2 + b_2 + a_{12}(y_{20} + y_{10}), \\ c &= b_2(a_1 + a_2) + b_2a_{12}(y_{20} + y_{10}) + a_1a_2 + a_{12}(a_1y_{10} + a_2y_{20}), \\ d &= b_2a_1a_2 + a_{12}b_2(y_{20}a_2 + a_1y_{10}) + \alpha a_{12}y_{10}\rho_1, \\ h &= (1 - \alpha)a_{12}y_{10}\rho_1. \end{aligned} \quad (13)$$

The equilibrium point $X^* = (x_{10}, y_{10}, x_{20}, y_{20})^T$ is locally asymptotically stable if and only if all eigenvalues of (12) have negative real parts.

Because $b_1 > 0$ we will analyze the function:

$$\Delta(\lambda, \tau) = \lambda^3 + b\lambda^2 + c\lambda + d + \frac{h}{\tau} \int_0^\tau e^{-\lambda s} ds, \quad (14)$$

with $\lambda \in \mathbb{R}$.

We are going to show that the equilibrium point X^* undergoes a Hopf bifurcation. In this sense, we look for the existence of the purely imaginary roots of $\Delta(\lambda, \tau) = 0$. First, we verify if X^* is locally asymptotically stable when $\tau = 0$. In this case, the equation $\Delta(\lambda, \tau) = 0$ becomes:

$$\lambda^3 + b\lambda^2 + c\lambda + d + h = 0. \quad (15)$$

Because the coefficients of equation (15) are positive then according to the Routh-Hurwitz criterion we have:

Proposition 2. *When there is no delay, the equilibrium point X^* of system (1) is locally asymptotically stable if and only if*

$$cb > d + h,$$

where c, b, d, h are given by (13).

We are looking for the values τ_0 so that the equilibrium point X^* changes from local asymptotic stability to instability or vice versa. This is specific for the characteristic equation with pure imaginary solutions. Let $\lambda = \pm i\omega$ be these solutions. We assume $\omega > 0$. It is sufficient to look for $\lambda = i\omega$ root of $\Delta(\lambda, \tau) = 0$. Separating real and imaginary parts of $\Delta(i\omega, \tau) = 0$ we obtain:

$$\sin(\omega\tau) = \frac{\tau\omega(b\omega^2 - d)}{h}, \quad \cos(\omega\tau) = 1 - \frac{\tau\omega^2(c - \omega^2)}{h}. \quad (16)$$

A solution of (16) is a pair (ω, τ) so that $\omega\tau \in [0, 2\pi]$, $\omega \in (0, \sqrt{c}]$ and $\tau = g_1(\omega)$, where $g_1 : [0, \sqrt{c}] \rightarrow \mathbb{R}_+$ is given by:

$$g_1(x) = \frac{2h(c - x^2)}{(bx^2 - d)^2 + x^2(c - x^2)^2}. \quad (17)$$

From (17) it results that $g_1(x) \in [0, \frac{2hc}{d^2}]$ and for all $\tau \in [0, \frac{2hc}{d^2}]$ there is $\omega \in [0, \sqrt{c}]$ so that $\tau = g_1(\omega)$.

We have:

Proposition 3. *For $\tau \in [0, \frac{2hc}{d^2}]$ there is $\omega \in [0, \sqrt{c}]$, so that (ω, τ) is solution of (16).*

According to the above proposition, system (16) has not unique solution.

In order to show that X^* undergoes a Hopf bifurcation for $\tau = \tau_0$ we have to prove that $\pm i\omega_0$ are simple eigenvalues of $\Delta(\lambda, \tau_0)$ and satisfy the transversality condition $\frac{d\operatorname{Re}(\lambda)}{d\tau}|_{\tau=\tau_0} \neq 0$.

From (14), it results that:

$$\Delta_\lambda(\lambda, \tau) = \frac{\partial \Delta}{\partial \lambda}(\lambda, \tau) = 3\lambda^2 + 2b\lambda + c - \frac{h}{\lambda^2 \tau}(1 - (1 + \lambda\tau)e^{-\lambda\tau}). \quad (18)$$

From (18), for (ω, τ) a solution of (16) and $\tau = g(\omega)$ it results that:

$$\begin{aligned} M_1 &= \operatorname{Re}(\Delta_\lambda(i\omega, g_1(\omega))) = -4\omega^2 + 2c - \tau(b\omega^2 - d) \\ M_2 &= \operatorname{Im}(\Delta_\lambda(i\omega, g_1(\omega))) = \frac{3b\omega^2 - d - h}{\omega} + \tau\omega(c - \omega^2). \end{aligned}$$

Then, we have:

$$\begin{aligned} M_1^2 + M_2^2 &= (2c - 4\omega^2)^2 + \tau^2(b\omega^2 - d)^2 + \frac{(3b\omega^2 - d - h)^2}{\omega^2} + \tau^2\omega^2(c - \omega^2)^2 + \\ &\quad + 2\tau((3b\omega^2 - d - h)(c - \omega^2) - (b\omega^2 - d)(2c - 4\omega^2)). \end{aligned} \quad (19)$$

From (19), it results that:

Proposition 4. If $bc > d + h$, $d > h$, $bc > 3d - h$, then $\lambda = i\omega_0$ is a simple root for the equation $\Delta(\lambda, \tau_0) = 0$.

Now, we consider a branch of eigenvalues $\lambda(\tau) = \nu(\tau) + i\omega(\tau)$ of (14) so that $\nu(\tau_0) = 0$ and $\omega(\tau_0) = \omega_0$, where (ω_0, τ_0) is a solution of (16). Differentiating equation $\Delta(\lambda(\tau), \tau) = 0$ with respect to τ , we obtain:

$$\lambda'(\tau) = \frac{d\lambda}{d\tau}|_{\tau=\tau_0, \omega=\omega_0} = -\frac{\Delta_\tau(i\omega_0, \tau_0)}{\Delta_\lambda(i\omega_0, \tau_0)} = M(\omega_0, \tau_0) + iN(\omega_0, \tau_0)$$

where

$$M(\omega_0, \tau_0) = -\frac{M_1 N_1 + M_2 N_2}{M_1^2 + M_2^2} \quad (20)$$

with

$$\begin{aligned} N_1 &= \frac{1}{\tau}[h - (b\omega^2 - d) - \tau\omega^2(c - \omega^2)] \\ N_2 &= \frac{1}{\tau}[\omega(c - \omega^2) - \tau\omega(b\omega^2 - d)] \end{aligned}$$

and

$$N = \frac{M_1 N_2 - M_2 N_1}{M_1^2 + M_2^2}. \quad (21)$$

By direct calculation $M \neq 0$.

We can conclude that when $\tau_0 \in [0, \frac{2hc}{d^2}]$ the characteristic equation $\Delta(\lambda, \tau_0) = 0$ has a unique pair of purely imaginary simple eigenvalues satisfied $\frac{dRe\lambda(\tau)}{d\tau}|_{\tau=\tau_0} \neq 0$ and the real roots are negative. Consequently, a Hopf bifurcation occurs at X^* when $\tau = \tau_0$. Moreover, applying Rouché's theorem we can verify that every eigenvalue of $\Delta(\lambda, \tau) = 0$ with $\tau < \tau_0$ has negative real part. It follows that X^* is locally asymptotically stable for $0 \leq \tau < \tau_0$. These results are summed up in the following theorem:

Theorem 1. *Assume that $cb > d + h$. Then there exists values $\tau_0 \in [0, \frac{2hc}{d^2}]$ of time delay so that the equilibrium point X^* is locally asymptotically stable when $\tau \in [0, \tau_0)$ and becomes unstable when $\tau = \tau_0$ throughout a Hopf bifurcation. In particular, the periodic solutions appear for system (1) when $\tau = \tau_0$.*

3. Direction and stability of the Hopf bifurcation

In the previous section, we obtain some conditions with guarantee that system (1) undergoes Hopf bifurcation at $\tau = \tau_0$.

In this section, we study the direction, the stability and the period of the bifurcating periodic solutions. The used method is based on the normal form theory and the center manifold theorem introduced by Hassard [6].

For an interval $I \subseteq \mathbb{R}$, we define the space of continuous functions as $C(I, K) = \{f : I \rightarrow K, f \text{ continuous}\}$, where $K = \mathbb{R}^4$ or \mathbb{C}^4 . When $I = [-\tau, 0]$, $\tau = \tau_0 + \mu$, $\mu > 0$ sufficiently small, we set $C_\mu = C([-\tau, 0], K)$. Expanding the functions from the right side of system (9) in Taylor series around $(0, 0, 0, 0)^T$ it results that:

$$\dot{X}(t) = AX(t) + \frac{1}{\tau}B \int_0^\tau X(t-s)ds + F(X(t), \int_0^\tau (\alpha X(t) + (1-\alpha)X(t-s))ds) \quad (22)$$

where

$$X(t) = (u_1(t), u_2(t), u_3(t), u_4(t))^T,$$

$$\int_0^\tau X(t-s)ds = (\int_0^\tau u_1(t-s)ds, \int_0^\tau u_2(t-s)ds, \int_0^\tau u_3(t-s)ds, \int_0^\tau u_4(t-s)ds)^T,$$

$$\begin{aligned} F(X(t), \int_0^\tau (\alpha X(t) + (1-\alpha)X(t-s))ds) &= (0, F^2(u_2(t), u_4(t)), \\ F^3(\int_0^\tau (\alpha u_2(t) + (1-\alpha)u_2(t-s))ds, F^4(u_2(t), u_4(t)))^T, \end{aligned} \quad (23)$$

$$\begin{aligned} F^2(u_2(t), u_4(t)) &= -a_{12}u_2(t)u_4(t), \\ F^3(\int_0^\tau (\alpha u_2(t) + (1-\alpha)u_2(t-s))ds) &= \frac{1}{2\tau}\rho_2 \int_0^\tau (\alpha u_2(t) + (1-\alpha)u_2(t-s))^2 ds + \\ &+ \frac{1}{6\tau}\rho_3 \int_0^\tau (\alpha u_2(t) + (1-\alpha)u_2(t-s))^3 ds, \\ F^4(u_2(t), u_4(t)) &= -a_{12}u_2(t)u_4(t), \end{aligned}$$

$\rho_2 = f''(y_{10})$, $\rho_3 = f'''(y_{10})$ and A,B are given by (11).

For $\Phi \in C_\mu$ with $K = \mathbb{C}^4$ we define a linear operator:

$$L_\mu(\Phi) = A\Phi(0) - \frac{1}{\tau_0}B \int_{-\tau_0}^0 \Phi(s)ds$$

and a nonlinear operator:

$$F_\mu(\Phi) = (0, F^2(\Phi_2(0), \Phi_4(0)), F^3(\int_{-\tau}^0 \Phi_2(s)ds), F^4(\Phi_2(0), \Phi_4(0)))^T.$$

For $\Phi \in C^1([-\tau_0, 0], \mathbb{C}^4)$ we define:

$$\begin{aligned} \mathcal{A}(\mu)\Phi(\theta) &= \begin{cases} \frac{d\Phi(\theta)}{d\theta}, & \theta \in [-\tau_0, 0) \\ A\Phi(0) - \frac{1}{\tau_0}B \int_{-\tau_0}^0 \Phi(s)ds, & \theta = 0, \end{cases} \\ R(\mu)\Phi(\theta) &= \begin{cases} 0, & \theta \in [-\tau_0, 0) \\ F_\mu(\Phi), & \theta = 0 \end{cases} \end{aligned}$$

and for $\Psi \in C^1([0, \tau_0], \mathbb{C}^{*4})$, we define the adjoint operator \mathcal{A}^* of \mathcal{A} by:

$$\mathcal{A}^*\Psi(s) = \begin{cases} -\frac{d\Psi(s)}{ds}, & s \in (0, \tau_0] \\ A\Psi(0) + \frac{1}{\tau_0}(\int_0^{\tau_0} \Psi(\theta)d\theta)B, & s = 0. \end{cases}$$

Then, we can rewrite (22) in the following vector form:

$$\dot{X}_t = A(\mu)X_t + R(\mu)X_t \quad (24)$$

where $X_t = X(t + \theta)$ for $\theta \in [-\tau_0, 0]$. For $\Phi \in C([-\tau_0, 0], \mathbb{C}^{*4})$ and $\Psi \in C([0, \tau_0], \mathbb{C}^{*4})$ we define the following bilinear form:

$$\langle \Psi(s), \Phi(\theta) \rangle = \bar{\Psi}(0)\Phi(0) - \int_{-\tau_0}^0 \int_{\xi=0}^{\theta} \bar{\Psi}(\xi - \theta) B \left(\frac{1}{\tau_0} \int_0^{\xi} \Phi(\xi') d\xi' \right) d\xi d\theta,$$

$s \in [0, \tau_0]$, $\theta \in [-\tau_0, 0]$.

Then, it can be verified that \mathcal{A}^* and $\mathcal{A}(0)$ are adjoint operators with respect to this bilinear form.

In the light of the obtained results in the last section, we assume that $\pm i\omega_0$ are eigenvalues of $\mathcal{A}(0)$. Thus, they are also eigenvalues of \mathcal{A}^* . We can easily obtain:

$$\Phi(\theta) = v e^{\lambda_1 \theta}, \quad \theta \in [-\tau_0, 0] \quad (25)$$

where $v = (v_1, v_2, v_3, v_4)^T$,

$$\begin{aligned} v_1 &= 0, v_2 = a_{12}y_{10}, v_3 = a_{12}^2 y_{10} y_{20} - (\lambda_1 + a_1 + a_{12}y_{20})(\lambda_1 + a_2 + a_{12}y_{10}), \\ v_4 &= -(\lambda_1 + a_1 + a_{12}y_{20}) \end{aligned}$$

is the eigenvector of $\mathcal{A}(0)$ corresponding to $\lambda_1 = i\omega_0$ and

$$\Psi(s) = w e^{\lambda_1 s}, \quad s \in [0, \tau_0]$$

where $w = (w_1, w_2, w_3, w_4)$,

$$\begin{aligned} w_1 &= \frac{1}{\bar{\eta}}, w_2 = \frac{d_2}{\bar{\eta}}, w_3 = \frac{d_3}{\bar{\eta}}, w_4 = \frac{d_4}{\bar{\eta}}, \\ d_2 &= b_1 + \lambda_1, d_3 = -\frac{a_{12}y_{10}(b_1 + \lambda_1)}{(\lambda_1 + a_2 + a_{12}y_{10})(b_2 + \lambda_1)}, d_4 = -\frac{a_{12}y_{10}(b_1 + \lambda_1)}{\lambda_1 + a_2 + a_{12}y_{10}} \\ \eta &= v_2 \bar{d}_2 + v_3 \bar{d}_3 + v_4 \bar{d}_4 - \bar{d}_3 v_2 \frac{(1 - \alpha)\rho_1}{\tau_0 \lambda_1^3} (\tau_0 \lambda_1 - 2 + 2e^{-\lambda_1 \tau_0} + \lambda_1 \tau_0 e^{-\lambda_1 \tau_0}) \end{aligned}$$

is the eigenvector of \mathcal{A}^* corresponding to $\lambda_2 = -i\omega_0$.

We can verify that: $\langle \Psi(s), \Phi(s) \rangle = 1$, $\langle \Psi(s), \bar{\Phi}(s) \rangle = \langle \bar{\Psi}(s), \Phi(s) \rangle = 0$, $\langle \bar{\Psi}(s), \bar{\Phi}(s) \rangle = 1$.

Using the approach in [1], we next compute the coordinates to describe the center manifold Ω_0 at $\mu = 0$. Let $X_t = X(t + \theta)$, $\theta \in [-\tau_0, 0]$, be the solution of equation (24) when $\mu = 0$ and

$$z(t) = \langle \Psi, X_t \rangle, \quad w(t, \theta) = X_t(\theta) - 2\text{Re}\{z(t)\Phi(\theta)\}.$$

On the center manifold Ω_0 , we have:

$$w(t, \theta) = w(z(t), \bar{z}(t), \theta)$$

where

$$w(z, \bar{z}, \theta) = w_{20}(\theta) \frac{z^2}{2} + w_{11}(\theta) z\bar{z} + w_{02}(\theta) \frac{\bar{z}^2}{2} + w_{30}(\theta) \frac{z^3}{6} + \dots$$

in which z and \bar{z} are local coordinates for the center manifold Ω_0 in the direction of Ψ and $\bar{\Psi}$ and $w_{02}(\theta) = \bar{w}_{20}(\theta)$.

For solution X_t of equation (24), as long as $\mu = 0$, we have:

$$\dot{z}(t) = \lambda_1 z(t) + g(z, \bar{z}) \quad (26)$$

where

$$\begin{aligned} g(z, \bar{z}) &= \bar{\Psi}(0) F(w(z, \bar{z}, 0) + Re(z\Phi(0))) = \\ &= g_{20} \frac{z^2}{2} + g_{11} z\bar{z} + g_{02} \frac{\bar{z}^2}{2} + g_{21} \frac{z^2 \bar{z}}{2} + \dots \end{aligned} \quad (27)$$

From (23), (26) and (27) we obtain:

$$\begin{aligned} g_{20} &= F_{20}^2 \bar{w}_2 + F_{20}^3 \bar{w}_3 + F_{20}^4 \bar{w}_4, g_{11} = F_{11}^2 \bar{w}_2 + F_{11}^3 \bar{w}_3 + F_{11}^4 \bar{w}_4, \\ g_{02} &= F_{02}^2 \bar{w}_2 + F_{02}^3 \bar{w}_3 + F_{02}^4 \bar{w}_4, \end{aligned} \quad (28)$$

where

$$\begin{aligned} F_{20}^2 &= F_{20}^4 = -2a_{12}v_2v_4, F_{11}^2 = F_{11}^4 = -a_{12}(v_2\bar{v}_4 + \bar{v}_2v_4), \\ F_{02}^2 &= F_{02}^4 = -2a_{12}\bar{v}_2\bar{v}_4 \\ F_{20}^3 &= \frac{\rho_2 v_2^2}{2\tau_0 \lambda_1} (2\alpha^2 \tau_0 \lambda_1 - 4\alpha(1-\alpha)(e^{-\lambda_1 \tau_0} - 1) - (1-\alpha)^2(e^{-2\lambda_1 \tau_0} - 1)) \\ F_{11}^3 &= \frac{\rho_2 v_2 \bar{v}_2}{\tau_0 \lambda_1 \lambda_2} (\lambda_1 \lambda_2 (\alpha^2 + (1-\alpha)^2) \tau_0 - \alpha(1-\alpha)(\lambda_2 e^{-\lambda_1 \tau_0} + \lambda_1 e^{-\lambda_2 \tau_0})) \\ F_{02}^3 &= \frac{\rho_2 \bar{v}_2^2}{2\tau_0 \lambda_2} (2\alpha^2 \tau_0 \lambda_2 - 4\alpha(1-\alpha)(e^{-\lambda_2 \tau_0} - 1) - (1-\alpha)^2(e^{-2\lambda_2 \tau_0} - 1)) \end{aligned}$$

and

$$g_{21} = F_{21}^2 \bar{w}_2 + F_{21}^3 \bar{w}_3 + F_{21}^4 \bar{w}_4 \quad (29)$$

where

$$\begin{aligned}
F_{21}^2 &= F_{21}^4 = -a_{12}\bar{v}_2w_{20}^4(0) - 2a_{12}v_2w_{11}^4(0) - a_{12}\bar{v}_4w_{20}^2(0) - 2a_{12}v_4w_{11}^2(0) \\
F_{21}^3 &= \frac{\rho_2}{\tau_0}(2v_2(\alpha^2\tau_0w_{11}^2(0) + \alpha(1-\alpha)k_1 - \frac{\alpha(1-\alpha)w_{11}^2(0)}{\lambda_1}(e^{-\lambda_1\tau_0} - 1) + \\
&+ (1-\alpha)^2k_2) + 2\bar{v}_2(\alpha^2\tau_0w_{20}^2(0) - \frac{\alpha(1-\alpha)}{\lambda_2}w_{20}^2(0)(e^{-\lambda_1\tau_0} - 1) + \\
&+ \alpha(1-\alpha)k_3 + (1-\alpha)^2k_4)) + \\
&+ \frac{\rho_3}{\tau_0}v_2^2\bar{v}_2^2(\alpha^3\tau_0 - \frac{(1-\alpha)^2\alpha}{2\lambda_1}(e^{-2\lambda_1\tau_0} - 1) - \frac{(1-\alpha)\alpha^2}{\lambda_2}(e^{-\lambda_2\tau_0} - 1) + (1-\alpha)^3\tau_0)
\end{aligned}$$

with

$$\begin{aligned}
k_1 &= \int_0^{\tau_0} w_{11}^2(-s)ds, k_2 = \int_0^{\tau_0} e^{-\lambda_1 s} w_{11}^2(-s)ds, \\
k_3 &= \int_0^{\tau_0} w_{20}^2(-s)ds, k_4 = \int_0^{\tau_0} e^{-\lambda_2 s} w_{20}^2(-s)ds \\
w_{20}^2(-s) &= -\frac{g_{20}}{\lambda_1}v_2e^{-\lambda_1 s} - \frac{\bar{g}_{02}}{3\lambda_1}\bar{v}_2e^{-\lambda_2 s} + E_2^2e^{-2\lambda_1 s} \\
w_{11}^2(-s) &= \frac{g_{11}}{\lambda_1}v_2e^{-\lambda_1 s} - \frac{\bar{g}_{11}}{\lambda_1}\bar{v}_2e^{-\lambda_2 s} + E_1^2 \\
w_{20}^2(0) &= -\frac{g_{20}}{\lambda_1}v_2 - \frac{\bar{g}_{02}}{3\lambda_1}\bar{v}_2 + E_2^2 \\
w_{11}^2(0) &= \frac{g_{11}}{\lambda_1}v_2 - \frac{\bar{g}_{11}}{\lambda_1}\bar{v}_2 + E_1^2 \\
w_{20}^4(0) &= -\frac{g_{20}}{\lambda_1}v_4 - \frac{\bar{g}_{20}}{3\lambda_1}\bar{v}_4 + E_2^4 \\
w_{11}^4(0) &= \frac{g_{11}}{\lambda_1}v_4 - \frac{\bar{g}_{11}}{\lambda_1}\bar{v}_4 + E_1^4,
\end{aligned} \tag{30}$$

$s \in [0, \tau_0]$, E_1^2, E_1^4 respectively E_2^2, E_2^4 are the components of the vectors:

$$\begin{aligned}
E_2 &= -(A - \frac{1}{2\lambda_1\tau_0}(e^{-2\lambda_1\tau_0} - 1)B - 2\lambda_1 I)^{-1}F_{20} \\
E_1 &= -(A + B)^{-1}F_{11},
\end{aligned}$$

where $F_{20} = (0, F_{20}^2, F_{20}^3, F_{20}^4)^T$, $F_{11} = (0, F_{11}^2, F_{11}^3, F_{11}^4)^T$.

Based on the above analysis and calculation, we can see that each g_{ij} in (28), (29) is determined by the parameters and delay from system (1). Thus,

we can explicitly compute the following quantities:

$$\begin{aligned} C_1(0) &= \frac{i}{2\omega_0}(g_{20}g_{11} - 2|g_{11}|^2 - \frac{1}{3}|g_{02}|^2) + \frac{g_{21}}{2} \\ \mu_2 &= -\frac{Re(C_1(0))}{M(\omega_0, \tau_0)}, T_2 = -\frac{Im(C_1(0)) + \mu_2 N(\omega_0, \tau_0)}{\omega_0}, \beta_2 = 2Re(C_1(0)), \end{aligned} \quad (31)$$

where $M(\omega_0, \tau_0)$, $N(\omega_0, \tau_0)$ are given by (20) and (21).

In summary, this leads to the following result:

Proposition 5. *In formulas (31), μ_2 determines the direction of the Hopf bifurcation: if $\mu_2 > 0 (< 0)$, then the Hopf bifurcation is supercritical (subcritical) and the bifurcating periodic solutions exist for $\tau > \tau_0 (< \tau_0)$; β_2 determines the stability of the bifurcating periodic solutions: the solutions are orbitally stable (unstable) if $\beta_2 < 0 (> 0)$; and T_2 determines the period of the bifurcating periodic solutions: the period increases (decreases) if $T_2 > 0 (< 0)$.*

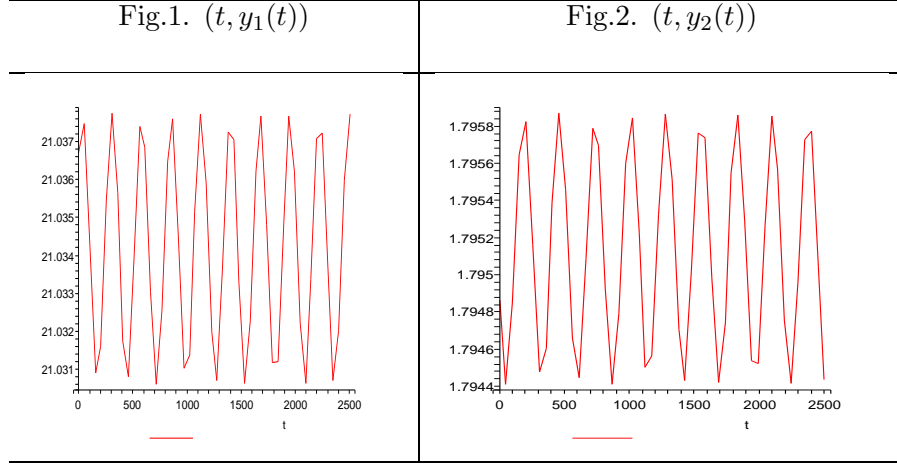
4. Numerical examples.

For the numerical simulations we use Maple 9.5. In this section, we consider system (1) with $a_1 = a_2 = 0.13$, $a_{12} = 0.02$, $a_{12} = 0.06$, $b_1 = 0.2$, $b_2 = 0.4$, $a = 4$, $\alpha = 0.2$, $n = 3$. Waveform plot are obtained by the formula:

$$X(t+\theta) = z(t)\Phi(\theta) + \bar{z}(t)\bar{\Phi}(\theta) + \frac{1}{2}w_{20}(\theta)z^2(t) + w_{11}(\theta)z(t)\bar{z}(t) + \frac{1}{2}w_{02}(\theta)\bar{z}(t)^2 + X_0,$$

where $z(t)$ is the solution of (26), $\Phi(\theta)$ is given by (25), $w_{20}(\theta)$, $w_{11}(\theta)$, $w_{02}(\theta)$ are given by (30) and $X_0 = (x_{10}, y_{10}, x_{20}, y_{20})^T$ is the equilibrium state.

We obtain: $x_{10} = 5$, $y_{10} = 21.03417191$, $y_{20} = 1.795140515$, $x_{20} = 2.498925919$, $\mu_2 = -0.2101567953$, $\beta_2 = -0.3029980114$, $T_2 = 0.1148699183$, $\omega = 0.1$, $\tau = 0.1001651263$. Then the Hopf bifurcation is subcritical, the solutions are orbitally stable and the period of the solution is increasing. The wave plots are displayed in fig1 and fig2:



5. Conclusions.

As in our previous model [9], we obtain an oscillatory behavior similar to that observed experimentally [3]. The conclusion is not surprising, but is useful as this model provides a more accurate approach of the interaction p53-mdm2. We can conclude that the transformation made by us to the continuous model with distributed time of the interaction p53-mdm2, which actually is more real, did not alter the behavior of the system.

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